

## Clinicopathological Aspects of Breast Cancer:

### A joint study between Indonesia and Japan

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#### Abstrak

Masalah penatalaksanaan klinik dari kanker payudara tetap penting dalam hal diagnosis dan pengobatan. Telah disarankan oleh penelitian-penelitian terdahulu bahwa perlu dipikirkan dua subset kanker payudara, yaitu penyakit yang agresif dan yang pertumbuhannya tidak nyata secara klinis (indolen). Oleh karena itu, penelitian aspek klinikopatologik kanker payudara berkaitan dengan fenomena semacam itu menjadi penting untuk dilakukan pada wanita Indonesia juga. Bersamaan dengan penelitian epidemiologik secara kasus-kontrol 300 kasus kanker payudara telah dianalisa terhadap aspek klinikopatologiknya. Semua kasus dievaluasi secara klinis menggunakan klasifikasi intemasional TNM dan Manchester yang baku dan secara histopatologik menggunakan modifikasi klasifikasi WHO seperti yang dianjurkan oleh Perhimpunan Kanker Payudara Jepang. Protokol penatalaksanaan kanker payudara dari Perhimpunan Ahli Bedah Onkologi Indonesia yang disesuaikan dengan pedoman yang diterima secara luas diterapkan seperlunya. Hasilnya menunjukkan bahwa kasus-kasus kanker payudara paling sering ditemukan pada golongan umur dibawah 35 tahun dan di antara 40 dan 44 tahun. Sebagian besar (87 %) pada stadium lanjut (stadium IJIA, IIIB dan IV) sedangkan hanya 13 % pada kanker stadium dini (stadium I dan II). Di antara 300 kasus hanya 110 kasus yang operabel. Prosedur bedah yang diterapkan adalah sebagai berikut: mastektomi radikal pada 50 kasus (16.6 %), mastektomi sederhana pada 40 kasus (13.37 %) dan bedah konservasi payudara pada 2 kasus (0.67 %). Kejangkitan kelenjar getah bening ditemukan pada 20 dari 50 kasus dengan mastektomi radika dan jumlah rata-rata kelenjar getah bening yang didiseksi adalah 6.8. Sebagian besar (88.33 %) adalah karsinoma duktal invasif dan sisanya jenis khusus (9.67 %) dan karsinoma non-invasif (1.33 %). Dua kasus (0.67 %) adalah penyakit Paget payudara. Di antara karsinoma duktal invasif jenis skirus merupakan jenis yang paling sering (49 %).

#### Abstracts

The problem of clinical management of breast cancer remains important in respect to both diagnosis and treatment. It has been suggested from earlier studies that two subsets of breast cancer might be considered, namely the aggressive disease and the indolent one. Therefore, the study of clinicopathological aspects of breast cancer in respect to such phenomena became important to be conducted in Indonesian females as well. In parallel to the epidemiological case-control study, 300 breast cancer cases have been analyzed for their clinicopathological aspects. All cases were evaluated clinically using standard International TNM and Manchester Classification and histopathologically using modified WHO classification as recommended by the Japanese Breast Cancer Society. Breast cancer management protocols of the Indonesian Surgical Oncology Association as adapted from the widely accepted standards were applied accordingly. The results showed that the breast cancer cases were mostly found in the age group under 35 years and between 40 to 44 years. The majority (87 %) were in advanced stage (stage II/A, IIIB and IV) while only 13 % were in early stage (stage I, II). Out of 300 cases only 110 cases were operable. The surgical procedures which were applied were as follows: radical mastectomy on 50 cases (16.6 %), simple mastectomy on 40 cases (13.37 %) and breast conserving surgery on 2 cases (0.67 %). Lymph node involvement was found in 20 out of 50 cases with radical mastectomy, and the average number of dissected lymph nodes were 6.8. The majority (88.33 %) was of invasive ductal carcinoma and the rest were special types (9.67 %) and non-invasive carcinoma (1.33 %). Two cases (0.67 %) were Paget's disease of the breast. Among the invasive ductal carcinoma the scirrhous type was the most common type (49 %).

**Keywords:** breast cancer, clinicopathological aspects, surgical procedures

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Clinical management of breast cancer remains as an important problems, including its biology, diagnosis and treatment. It has been estimated that mortality amounted to 40 %.<sup>1</sup> Considerable increase of the breast cancer mortality has been observed in 28 developed countries from 1960 to 1980, with 22 % change.<sup>2</sup> The prognosis has been considered poor, with about 50 % 5-year relative survival and a 15-20 % overall long-term relative survival.<sup>3</sup> However, there

were appreciable differences between Japan and America, namely that breast cancer in Japanese women were in lower incidence rate (13.9 versus 73.9 per 100,000) and better prognosis.<sup>4</sup> In Indonesia, breast cancer ranked the second i.e. in the 1989 the relative frequency (age standardized cancer ratio) was 18 % in pathology based cancer registry from 13 pathology centers. and age adjusted incidence rate was 18.69 per 100,000 annually in regional population based cancer registry.<sup>7</sup>

It is of interest to study the similarity and the dissimilarity of the breast cancer problems between the Indonesian patients and the Japanese patients in a collaborative study.

This study was conducted to evaluate the clinicopathological aspects of breast cancer in Indonesian females in relation to the epidemiological study on risk factors in breast cancer.

The findings will be evaluated in respect to the response to therapy. In addition, the estrogen receptor status background was considered in the evaluation.

## METHODS

Three hundred female breast cancer patients were admitted for treatment at the Department of Surgery Dr. Cipto Mangunkusumo National General Hospital, Faculty of Medicine, University of Indonesia, Jakarta during the period of 1988 until 1991. All cases were clinically examined according to age, clinical stage and pathological stage, lymphnode involvement, treatment modality and estimation of metastasis at diagnosis. Cases were subjected to routine laboratory examinations. Other investigations such as chest X-ray skeletal X-ray and liver function test were also carried out in most instances.

In all cases histopathological examination was done and for clinical staging the International TNM Classification<sup>8-9</sup> was used (see Appendices 1 and 2). Based on the extent of the tumor growth and its metastasis the cases were also evaluated whether they were operable or non-operable.

All operable patients were appropriately treated with surgery alone or in combination with radiotherapy or chemotherapy, namely radical mastectomy, modified radical mastectomy and simple mastectomy, radiotherapy in combination with surgery, chemotherapy in combination with surgery and

radiotherapy as adjuvant therapy, according to Breast Cancer Management Protocol of the Indonesian Surgical Oncology Association (see Table 1).

The protocol was adapted from widely accepted procedures.<sup>10-14</sup>

## RESULTS

The age distribution of the 300 female breast cancer are given in Table 1.

The highest proportion of breast cancer cases were in the age group under 35 years and between 40-44 years. Lower peak was seen in the age group of 60-65 years.

Table 1. Age distribution of 300 female breast cancer

Age in years	No. of cases	%
< 35	51	17.0
35 - 39	34	11.3
40 - 44	51	17.0
45 - 49	42	14.0
50 - 54	29	9.6
55 - 59	26	8.6
60 - 65	46	15.3
70 +	12	4.0
	9	3.0
Total	300	100

The clinical staging revealed that 2.6 % were stage I, 10.3 % were stage II, 23.6 % were stage IIIA, 43 % were stage IIIB and 20.3 % were stage IV. The details are given in Table 2, showing the grouping of patients in respective stages of both the Manchester and UICC-TNM Classification. Twelve out of 31 cases of stage II were T2a N1a Mo. Thirty three and 32 cases out of 71 cases of stage IIIA were T3a N0 Mo and T3a N1a Mo respectively. The majority of stage IIIB were of T3b, T4a and T4b (14, 11 and 83 out of 129 cases respectively). Seventeen out of 61 cases of stage IV were T4a N1a M1 while 11 were T4a N1a Mi and 11 were T4a N2 Mi.

Out of 110 operable cases 92 patients underwent surgical treatment at the Dr. Cipto Mangunkusumo National General Hospital, while the rest (18 cases) were operated on at other private hospitals in Jakarta. Number of patients underwent respective surgical method performed, namely radical mastectomy, simple mastectomy or lumpectomy / breast conserving tumorectomy (BCF) are given in Table 3. Proportion of

Table 2. Clinical staging

The Manchester	UICC Classification			No. of cases	Total	%
Stage						
	T1o	No	Mo	4		
	T1b	N1.	Mo	4	8	2.6 %
<b>II</b>	T1a	No	Mo	6		
	T2b	No	Mo	4		
	Tz.	N1a	Mo	12	31	10.3 %
	T2b	N1a	Mo	2		
	T2c	N1b	Mo	7		
<b>IIIA</b>	TJ1a	No	Mo	33		
	TJ.	N1a	Mo	32		
	TJ1a	N1b	Mo	3		
	T4a	No	Mo	1	71	23.6 %
	T4a	N1b	Mo	2		
	T4a	N1	Mo	2		
<b>IIIB</b>	TJb	No	Mo	2		
	TJb	N1a	Mo	14		
	TJb	N1b	Mo	4		
	TJb	N2	Mo	3		
	TJb	NJ	Mo	1		
	T4a	NJ	Mo	11		
	T4b	No	Mo	13	129	43 %
	T4b	N1a	Mo	27		
	T4b	N1b	Mo	16		
	T4b	Nz	Mo	27		
	T4c	No	Mo	1		
	T4c	N1a	Mo	2		
	T4c	N1b	Mo	3		
	T4c	N2	Mo	5		
<b>IV</b>	TJb	N1a	Mt	2		
	TJb	N1b	M1	3		
	TJb	N2	M1	3		
	T4a	N1a	Mt	2		
	T4.	N1b	M1	3		
	T4a	N1a	M1	17		
	T4b	N1b	M1	6	61	20.3 %
	T4b	N1b	M1	3		
	T4c	N2	Mt	11		
	T4a	N1	Mt	11		
	T4c	N2	Mt	4		
	T4b	N1	Mt	4		
	T4c	Nz	M1	2		
	Total				300	

Among 50 cases with radical mastectomy, 20 cases showed lymphnodes involvement with positive metastasis and 30 cases showed lymphnodes involvement with negative metastasis. See also Table 4. Average number of dissected lymph nodes were 6.8 lymphnodes.

Table 4. Number of Radical Mastectomy cases with involvement of the regional lymphnodes

No. of total radical mastectomy cases	No. lymph nodes involvement positive metastasis	No. lymph nodes involvement negative metastasis
50	20	30

The operable cases were evaluated for their tumor site and the results can be seen in Table 5. Patients with radical mastectomy was higher than the one with simple mastectomy (16.6 % and 13.37 % of the total 300 breast cancer cases respectively. BCT was only performed on 2 cases.

Table 3. Number of patients of respective surgical method

Surgical method	No. of operable cases	Percentage (from all 300)
Radical mastectomy	50	16.6
Simple mastectomy	40	13.37
Lumpectomy / BCT	2	0.67
<b>Total</b>	<b>92</b>	

Most of breast cancers were found in the upper outer quadrant (73.9 %), followed by upper inner quadrant (10.8 %), lower inner quadrant (8.6 %), subareolar (4.3 %) and lower outer quadrant (2.1 %).

Table 5. Distribution of operable breast cancer cases according tumor site

Site	No. of cases	Percentage
Upper outer quadrant	68	73.9
Lower outer quadrant	2	2.1
Upper inner quadrant	10	10.5
Lower inner quadrant	8	8.6
Subareolar	4	4.3
<b>Total</b>	<b>92</b>	<b>100</b>

The results of histological typing on all 300 cases are given in Table 6. The majority were the invasive carcinoma, consisting mostly (88.33 %) of the invasive ductal carcinoma and 9.66 % of the special type, and the rest (1.33 %) were non-invasive carcinoma. Paget's disease were only found in 2 cases.

Table 6. Distribution of 300 breast cancer cases according to histological types

Histological types	Number of cases	%
Non invasive carcinoma:	4	1.33
a. Non invasive ductal carcinoma		
b. Lobular carcinoma in situ		
Invasive carcinoma		
a. <i>Invasive ductal carcinoma:</i>		
ai papillotubular	39	13.00
a2 solid tubular	79	26.33
a3 scirrhous	147	49.00
b. <i>Special types:</i>		
bi mucinous carcinoma	4	1.33
b1 medullary carcinoma	17	5.68
b3 invasive lobular carcinoma	7	2.33
b4 adenoid cystic carcinoma	1	0.33
Paget's disease	2	0.67

The histological typing was evaluated on 110 operable cases, as can be seen in Table 7. Similarly, the invasive ductal carcinoma were dominant, consisting of mostly (64.54 %) the scirrhous type, followed by 12.72 % of papillo-tubular type and 7.27 % of solid-tubular type. The rest were the special type (mucinous, medullary, lobular and adenoid cystic).

Table 7. Distribution of 110 operable cases of breast cancer according to histological types

Histological types	Number of cases	%
Invasive ductal papillo-tubular carcinoma	14	14.72
Invasive ductal solid tubular carcinoma	8	7.27
Invasive ductal scirrhous carcinoma	72	64.54
Mucinous carcinoma	2	1.81
Medullary carcinoma	6	5.45
Invasive lobular carcinoma	5	4.54
Adenoid cystic carcinoma	1	0.90
Paget's disease	2	1.81
<b>Total</b>	<b>110</b>	<b>100</b>

## DISCUSSION

The study on the age distribution of all breast cancer patients indicated that the breast cancer has already occurred in younger age, namely under 40 years, with relatively high proportion. Similar findings were seen in Jakarta<sup>1</sup> and in other geographical area of our country with rather different demographical composition i.e. East Java.<sup>16</sup> Such age distribution pattern was similar to that of Japanese women but differs considerably from other populations such as American women.<sup>4</sup>

The analysis of the stage of the disease has revealed that the majority (87 %) were in advanced stage (stage IIIA, IIIB and IV) while only 13 % were in early stage (stage I and II). The present findings were consistent with our previous data.<sup>15,17</sup> This was in contrast to the pattern of breast cancer in Japan, the majority of cases were in early stage.<sup>5</sup>

Out of 300 breast cancer patients only 110 cases were operable. The proportion of cases that need radical mastectomy was slightly higher than the simple mastectomy cases. Our previous study showed similar data even after 10-year survival observation.<sup>17</sup> Lumpectomy or breast conserving tumorectomy were only performed in 2 cases (0.67 %).

The evaluation on tumor site showed that the tumor occurred mostly (73.9 %) in the upper outer quadrant.

Histological typing on all 300 breast cancer cases has revealed that the majority were the invasive carcinoma, with predominance of invasive ductal type and small proportion of special type, while only 1.33 % were non-invasive carcinoma. Evaluation on 110 operable cases resulted in similar findings, i.e. mostly the invasive ductal carcinoma, two-third of which were the scirrhous type. The latter has been observed to show lower 10-year survival rate as compared to the other types i.e. papillo-tubular and medullary tubular carcinoma.<sup>5</sup> Paget's disease were only found in 2 cases.

Our data showed both similarity and dissimilarity between the breast cancer in Indonesian women and the Japanese women.<sup>18</sup> Our preliminary study of hormonal receptor expression in 50 Indonesian breast cancer cases indicated that 72% were estrogen receptor (ER) rich breast cancers. More than two-third of patients with moderate differentiation showed ER-positivity. Furthermore, it contributed to the evidence of subsets of breast cancer relative to its biological behavior, i.e. aggressive, indolent or in between. Further study needs elucidating related factors in respect to such difference in biological behavior.

Thus, we anticipated that clinicopathological study would take the benefit of related studies such as hormonal receptors (estrogen and progesteron receptors) and oncogenes (c-erbB-2 and p53). It has been reported recently that the expression of such molecular markers might influence the risk of tumor growth, the disease prognosis and the response to therapy.<sup>19,22</sup>

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**Appendix-I**

Breast cancer management protocol - Indonesian Surgical Oncology Association, December 1989

Stage I	N0-ta N0-1a	Mo Mo	Radical mastectomy or modified radical mastectomy If lymph node negative: observation only If lymph node positive: regional irradiation + adjuvant chemotherapy	
Stage II	To Mo T1a Mo T1b T1b T2a T1b	N1b Nib Nib N0-1a Nib Nib	Mo Mo Mo Mo Mo	Radical mastectomy or modified radical mastectomy with irradiation on tumor bed and regional lymph node
Stage III	Any T3 with any N Any T4 with any N Any T with N1 Any T with N3	Mo Mo Mo Mo	Stage III is divided into Stage IIIA and Stage IIIB	
Stage IIIA	T3a-4a T2a-2b	Mo Mo	Simple mastectomy with irradiation of tumor bed + regional lymph-node + chemotherapy as adjuvant therapy	
Stage IIIB	T3b-4b-4c any N	Mo	Considered as non-operable primary treatment is irradiation on tumor bed + lymphnode region + chemotherapy + hormonal therapy	
Stage IV	Any T any N with M1		Primary treatment is hormonal therapy. This is divided into 3 groups. 1. Premenopausal women -- castration / anti estrogen therapy 2. Women with 1-5 yr post menopausal status were evaluated for the estrogen activity on vaginal smear: If positive -- castration/or anti estrogen therapy If negative ....., considered as post menopausal case -- anti estrogen therapy 3. Women after 5 yrs post menopausal status -..... estrogen therapy  Estrogen and Progesteron receptor assessment in respect to the therapy is not yet done routinely in our Hospital	

## Notes:

Adjuvant chemotherapy is given with the regimen of CMF (6 cycles).

C = Cyclophosphamide orally 60-80 mg/m<sup>2</sup>/day, day 1 until day 14.M = Methotrexate 40 mg/m<sup>2</sup> i.v., day 1 and day 8.F = 5-Fluorouracil 600/m<sup>2</sup> i.v., day 1 and 8.

1 cycle = 28 days.

## Appendix-2

Breast Cancer Classification: TNM system (UICC)

Tumor size (T)

	Not palpable	≤ 2 cm	0! 2-5 cm	> 5 cm
No deep fixation	To	Tt	T2a	T3a
With fixation	Ttb	T2b	T3b	
Any size + direct chest extension				T4
Any size + skin infiltration or oedema				T4b
or peau d'orange or satellite nodule confined to same breast				T4a + T4b + = T4c

Nodal Status (N)

	No	Nia	Ntb	N1
Homolateral axillary nodes	Not palpable	Palpable	Palpable	Palpable
		Clinical non-malignant	Clinical malignant	Malignant fixed
Homolateral clavicular node(s) clinically malignant or oedema of anii				N3

Metastases (M)

Mo No clinically apparent distant metastases

Mt Distant metastases apparent

The Manchester / UICC Classification

Stage I	T1a T2a	No No	Mo
Stage II	To T1a T2a	Ni Ni Ni	Mo
Stage III	T3 To,1,2 Ttb, T2b T4	No,1,2 N2 No,1,2 No,1,2	Mo
Stage IV	Any T	N3 or	Mt